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REVIEW

'Time is prognosis' in heart failure: time-to-treatment initiation as a modifiable risk factor

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Abstract

In heart failure (HF), acute decompensation can occur quickly and unexpectedly because of worsening of chronic HF or to new-onset HF diagnosed for the first time ('*de novo*'). Patients presenting with acute HF (AHF) have a poor prognosis comparable with those with acute myocardial infarction, and any delay of treatment initiation is associated with worse outcomes. Recent HF guidelines and recommendations have highlighted the importance of a timely diagnosis and immediate treatment for patients presenting with AHF to decrease disease progression and improve prognosis. However, based on the available data, there is still uncertainty regarding the optimal 'time-to-treatment' effect in AHF. Furthermore, the immediate post-worsening HF period plays an important role in clinical outcomes in HF patients after hospitalization and is known as the 'vulnerable phase' characterized by high risk of readmission and early death. Early and intensive treatment for HF patients in the 'vulnerable phase' might be associated with lower rates of early readmission and mortality. Additionally, in the chronic stable HF outpatient, treatments are often delayed or not initiated when symptoms are stable, ignoring the risk for adverse outcomes such as sudden death. Consequently, there is a dire need to better identify HF patients during hospitalization and after discharge and treating them adequately to improve their prognosis. HF is an urgent clinical scenario along all its stages and disease conditions. Therefore, time plays a significant role throughout the entire patient's journey. Therapy should be optimized as soon as possible, because this is beneficial regardless of severity or duration of HF. Time lavished before treatment initiation is recognized as important modifiable risk factor in HF.

Keywords Heart failure; Treatment; Prognosis

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Introduction

Despite remarkable improvements in the management of cardiovascular diseases including heart failure (HF) during the last few decades, death due to cardiovascular diseases remains the leading global cause of mortality.[1] Cardiac events occur rapidly, and a significant number of patients die, rendering the prompt diagnosis and treatment into a challenging task to improve outcome.[1,2] Before the 1980s, ST-elevation myocardial infarction (STEMI) management was based on relieving pain and heart rate reduction to decrease cardiac work and oxygen consumption.[3,4] Subsequently, a revolutionary concept known as 'Time Is Muscle' was proposed by Eugene Braunwald.[4] When this concept was introduced, it provided a paradigm shift in the management of acute coronary syndromes with STEMI.[3–6] Based on the concept that the delay between symptom onset and first balloon inflation affects myocardial perfusion and clinical outcomes,[4–6] many

trials were prompted to judge quality of care as 'door-to-needle time' (thrombolysis) or 'door-to-balloon time' (coronary interventions).[7] This approach is widely accepted as standard of care of STEMI with timely treatment linked to improved outcomes.[7]

Chronic HF (CHF) is widely regarded as a chronic condition,[8] with particularly high and consistent increase in all epidemiological parameters making it as one of the most rapidly growing cardiovascular (CV) conditions. This results in a substantial burden on healthcare systems worldwide.[8,9] The connotation of the term 'chronic' HF might suggest that this syndrome does not require urgent treatment and there could be time to weigh up benefit and potential risks of outcome-improving drugs, to observe the natural course of symptoms and signs and to delay treatment initiation to the outpatient setting in a stable HF patient.[2,10] This approach does not take into consideration that an acute decompensation is associated with acute and potentially irreversible myocardial damage.[11–15] This damage is indicated by elevation of injury markers as seen in acute coronary syndromes,[13,16–18] with greater levels associated with worse outcomes.[18] After discharge following an episode of acute HF (AHF) worsening, high rates of rehospitalization and death have been recognized and the term 'vulnerable phase' of the HF syndrome was coined.[19,20] In these patients, outcome-modifying and guideline-recommended treatments often have not been introduced. This might be related to concerns, but not scrutiny, of intolerance to treatments or due to the 'evidentio-centric' view that outcome trials are only performed in stable outpatients following a definite time after discharge from the hospital and because post-discharge follow-up has been delayed, neglected, and/or not occurred in setting with adequate HF expertise. Furthermore, in the stable CHF outpatient, with 'provider inertia', treatments are often not maximized when symptoms are stable, despite evidence supporting ongoing titration.[20] The earlier after an episode of decompensation, the higher risk of hospitalization or death. Herein, we focus on the time factor of treatment initiation from acute decompensation to the treatment of the stable CHF patient. Although the clinical status is on a continuum, we identify three distinct phases: AHF, vulnerable phase (before and early after discharge), and CHF.

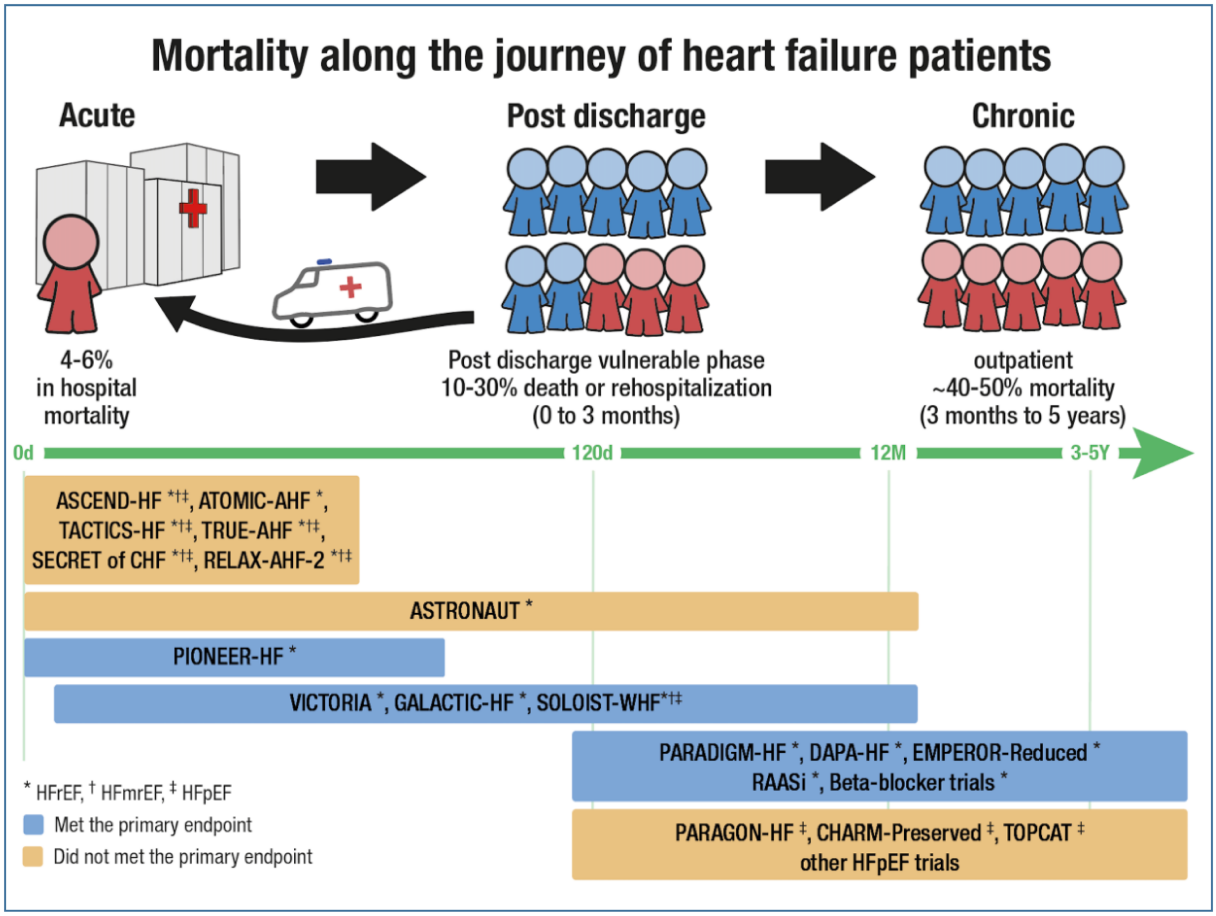
In-hospital treatment of patients with acute worsening of heart failure

Worsening of CHF accounts for 70–80% of those hospitalized with AHF, while only 20–30% have new-onset or advanced HF.[8,9] Presently, hospitalization due to AHF is still associated with poor outcomes, with in-hospital mortality of 4–6% and rehospitalization rates and 1 year mortality of 10–30%[8,9] (*Figure 1*).

In AHF, pathophysiological pathways are activated, which may initially be compensatory to maintain haemodynamics acutely, but with time become maladaptive.[19] Among those, neurohormonal activation such as activation of the sympathetic nervous and renin–angiotensin–aldosterone system leading to congestion, myocardial inflammation, and cellular interstitial and myocyte remodelling might be important.[19,28] Volume overload and congestion cause signs and symptoms of AHF[9,28] but impose wall stress on the heart, thereby damaging cardiomyocytes directly in concert with neurohormonal activation, leading to extracellular matrix accumulation and myocyte apoptosis and necrosis.[17–19] Thus, recent HF guidelines and recommendations highlighted the importance of urgent diagnosis and immediate treatment of AHF; however, specific timelines were not mentioned.[12–15]

Although an appropriate implementation is lacking, the concept of 'door-to-diuretic' (D2D) time is not novel. Around a decade ago, Maisel *et al*. first introduced the D2D time by analysing decompensated HF patients in the ED from the Acute Decompensated Heart Failure National Registry (ADHERE).[29,30] They demonstrated a significant association between each 4 h delay in initiation of diuretics and an increase in mortality. Another analysis from the same registry showed that hospital stay, need for intensive care unit, and symptoms at discharge were more prevalent in patients receiving late treatment.[10,31] However, these analyses were observational retrospective studies with no uniform estimation of the delay in treatment and of the therapy applied.[10,29] Approximately 20 years later, the first prospective registry to evaluate the association between time-to-diuretic treatment and clinical outcome was conducted.[11] In this analysis, 1291 patients with AHF presenting to the ED were included. The study assessed the association between D2D treatment and all-cause in-hospital mortality. The median time to intravenous diuretic was 90 min. The investigators then divided the subjects into early ($<$60 min) and later D2D times. Patients in the early treatment group presented with more prominent congestion and higher blood pressure than the later treated patients. In-hospital mortality was significantly lower in the early treatment group (2.3% vs. 6.0% in the late treatment group; P = 0.002). In multivariate analysis, earlier treatment remained significantly associated with lower in-hospital mortality (odds ratio: 0.39; 95% confidence interval: 0.20–0.76; P = 0.006). An optimal cut-off of 100 min from ED arrival was determined for predicted mortality, which steeply increased in the first 100 min and levelled off afterwards. The same question was addressed later among 5625 consecutive patients enrolled in the KorAHF [Registry (Prospective Cohort) for Heart Failure in Korea] registry hospitalized for AHF.[32] Patients were divided into early (D2D time $<$60 min) and delayed (D2D time $>$60 min) groups. The primary outcomes were

Figure 1 In-hospital mortality is high after acute decompensation (left, 4–6%). In the post-discharge phase, rehospitalization rate (depicted by arrow) and death are higher (10–30% death or rehospitalization) than in the chronic outpatient heart failure population (40–50% 5 year mortality). The figure shows landmark heart failure trials during the period where patients were included in those studies (in-hospital and pre-discharge, early post-hospitalization—vulnerable phase, and in the chronic phase). Also, this figure shows which trial did or did not meet its primary endpoints. Data taken from several studies.[8,9,21–23,24,25–27]

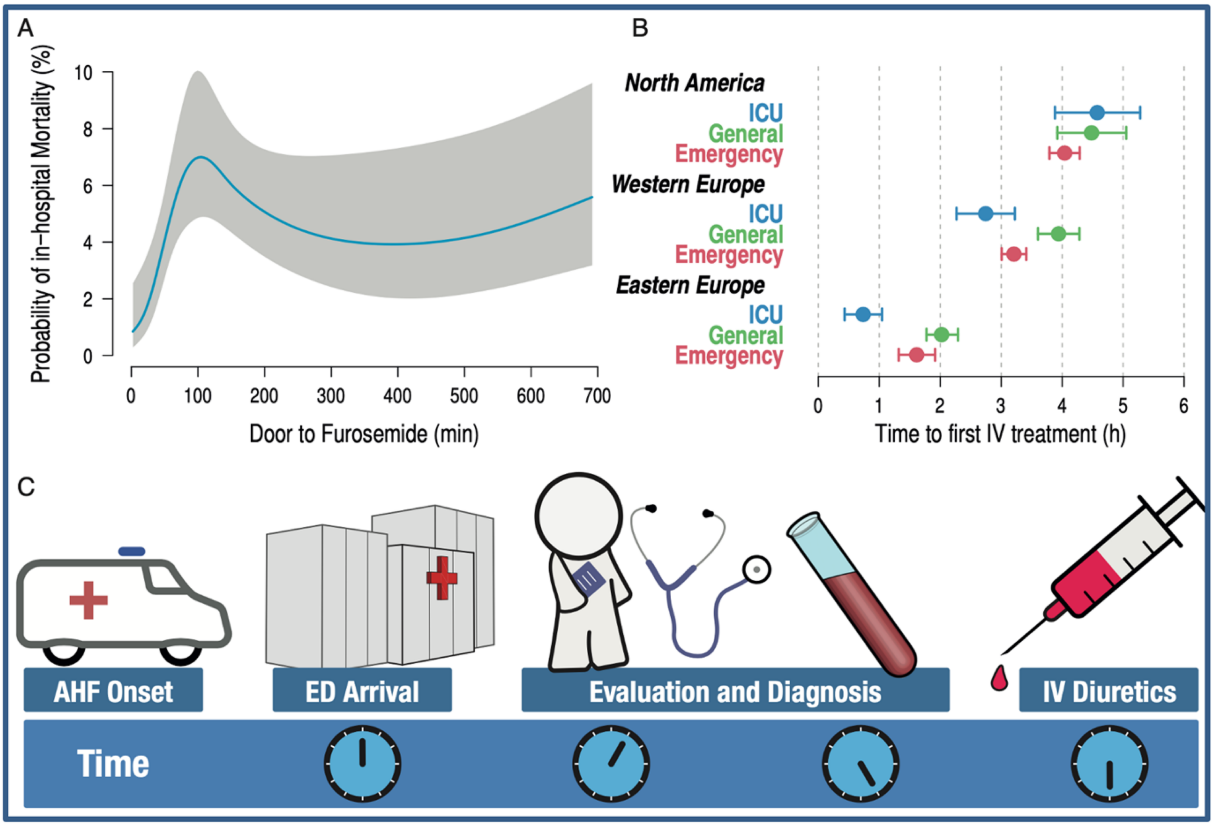


in-hospital death and post-discharge death at 1 month and 1 year on the basis of D2D time. Both groups had similar in-hospital and post-discharge outcomes. These results were not substantially changed by risk adjustment or propensity score matching to control for visible potential confounders. Very recently, the observational FAST-FURO study showed that early intravenous furosemide administration by emergency medical services during the prehospital phase in AHF patients who will require intravenous furosemide treatment at the ED was not associated with changes in short-term mortality or length of hospitalization after adjustment for several confounders.[33] However, the results of the previous studies should be evaluated carefully because of unavoidable confounding of observational data. Additionally, the complexity of HF diagnosis and different pathobiological mechanisms may lead to diverse presentation pictures. Notably, differences between studies results might be related to different medical practice and to varying densities of HF units and hospitals in different countries, and even in different regions within one country might affect mortality[2,34,35] (*Figure 2*).

Hitherto, no specific therapy was established to target the pathophysiological process in AHF beyond timely decongestion. This was also shown by the neutral mortality result from TRUE-AHF trial with ularitide[36] as well as from the RELAX-HF trial with serelaxin,[37] where effects beyond decongestion with diuretics could not be scrutinized.

All these data make it hard to believe that shorter D2D time is analogue to door-to-balloon time in STEMI. In brief, there is still uncertainty regarding the optimal D2D effect in AHF and whether rapid clinical decongestion might improve prognosis besides improving symptoms.

Figure 2 (A) Association of door-to-furosemide time with probability of in-hospital mortality. (B) Duration to time-to-first intravenous (IV) diuretic treatment on the intensive care unit (ICU), general ward, or emergency ward in North America (upper panel) Western Europe (middle panel) and Eastern Europe (lower panel). (C) Recommendation for a timely evaluation, diagnosis, and IV start of diuretic treatments after arrival in the emergency department (ED) after onset of acute heart failure (AHF) symptoms. Data taken from Matsue *et al.* and Filippatos *et al.*[11,34]



Pre-discharge and post-hospitalization vulnerable phase: time matters!

As HF represents a huge cost burden for healthcare systems globally, there is a huge need to reduce hospitalizations due to readmissions.[1,9] The ASCEND-HF registry studied patients with AHF according to variations of length of stay across countries.[38] It showed that readmission rates were significantly lower between patients treated in countries with longer lengths of stay for HF hospitalizations. After multivariable adjustment, each additional 1 day in the mean length of stay was independently associated with a lower risk of all-cause readmission by 14% and HF readmission by 21%.[38] This is in line with the strategy to take the time to decongest the patients as a priority in order to reduce readmission and mortality.[39] Many analyses have shown that patients with severe symptoms (New York Heart Association IV) have a 50% mortality risk within 1–2 years compared with 20–30% for Class III symptoms.[39,40] Patients who were well decongested at discharge had an improved survival despite previous Class IV symptoms at admission.[39]

Moreover, another strong predictor of mortality in HF patients is the number of previous HF hospitalizations. For example, 50% of patients die by 1 year after three hospitalizations.[41,42] This simple predictor of mortality in HF patients might help to triage patients to guide management and predict prognosis.[41] This in turn suggests that prevented hospitalizations could have an impact on subsequent mortality/hospitalizations. Although this concept needs to be scrutinized in adequately designed clinical trials, preventing HF hospitalization is an important therapeutic objective particularly in patients with CHF with reduced ejection fraction (HFrEF) as they still represent the majority of the HF population.[43] The risk of mortality and rehospitalization is clearly high in the early phase of hospitalization and remains elevated even after 18 months of discharge.[43] Based on the earlier, the immediate post-discharge period plays an important role in clinical outcomes in HF patients after hospitalization and has been suggested to be the vulnerable phase, including patients at high risk of readmission and early death.[20,44] The most likely potential mechanism for the poor prognosis is the persistent subclinical or manifested congestion at discharge.[44–48] Therefore, there is a need to better

identify these patients during hospitalization, to treat them intensively and early, on the basis this might be associated with lower rates of early readmission and mortality.[20,42–45]

Initiation and optimization of guideline-directed CHF therapy might be important for patients already at, or before discharge after hospitalization for HF worsening, to reduce early death and rehospitalization. However, randomized controlled clinical trials are usually performed in stable outpatients, thus not covering the vulnerable early post-discharge phase with few exceptions[21–23] (*Figure 1*). The majority of clinical trials performed during pre-discharge and post-hospitalization phase showed neutral results that did not meet its primary endpoints (*Figure 1*). These are sometimes used to argue that early intervention may not be helpful in the setting of AHF. However, this is a misused argument and should not be extrapolated to argue that therapies with strong evidence for CHF that may not have been studied in AHF should not be started as early as possible. Undertreatment at discharge might be also due to the reluctance of physicians to introduce guideline-recommended treatments as they reduce blood pressure and heart rate and as HF patients with low blood pressure have worse outcomes than those with higher blood pressure levels.[49–52] However, withholding of beta-blocker therapy after discharge in decompensated HF patients has been shown to be associated with an increased risk of post-discharge mortality.[53,54] Additionally, in euvolemic patients with symptoms at rest or on minimal exertion (New York Heart Association III–IV), the addition of carvedilol to conventional therapy ameliorates the severity of HF and reduces the risk of clinical deterioration, hospitalization, and other serious adverse clinical events.[55] Moreover, starting with HF oral therapy at hospital discharge is associated with a significantly better outcome of AHF patients regardless of associated co-morbidities.[48] The GREAT registry[48] demonstrated that treatment with oral HF therapy including beta-blockers, renin–angiotensin system inhibitors, and mineralocorticoid receptor antagonist in the hospital and before discharge provided better outcomes compared with deferring the treatment initiation in post-AHF patients.

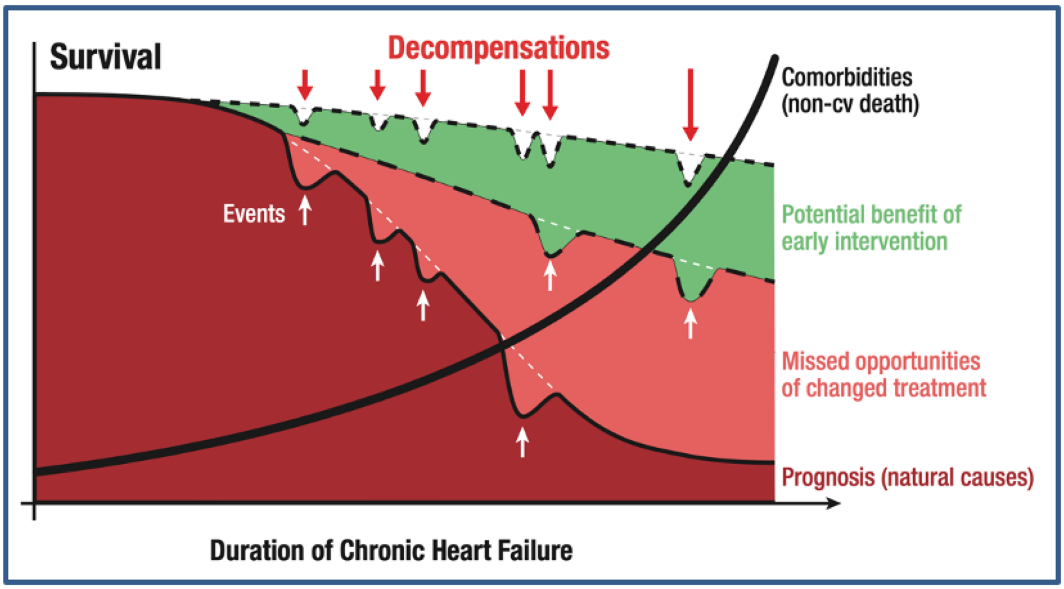
Furthermore, optimizing HF therapy during hospitalization covering the vulnerable phase early after discharge improves outcomes.[20] CV death or hospitalizations for worsening HF increased by 3% with every beat per minute (b.p.m.) increase from baseline heart rate and 16% for every 5 b.p.m. increase with a direct association between lower heart rate achieved after treatment initiation at 28 days and subsequently reduced cardiac outcomes.[56] In agreement with this, initiation of ivabradine and beta-blockers during AHF hospitalization leads to improved haemodynamics by a sufficient decrease in heart rate[56–58] and subsequently improves clinical parameters of HF patients at short term.[57,58] The PIONEER-HF trial included patients during hospitalization for acute decompensated HF. Sacubitril/valsartan led to a greater unloading of the heart suggested by a stronger reduction of N-terminal pro-brain natriuretic peptide concentration and a reduction of exploratory outcomes (HF rehospitalizations, death, and heart transplantation) compared with enalapril therapy without safety concerns.[22] Risk reduction was present as early as 1 week after drug initiation in enalapril-pretreated and naïve patients.[22] Notably, this trial was not powered for clinical endpoints but still provides signals for risk reduction. Data pointing in the same direction are available for other HF drugs. Very recently, the SOLOIST-WHF trial showed that patients with diabetes and recent worsening HF were treated with sotagliflozin, which was initiated before or shortly after discharge resulting in a significantly lower total number of CV deaths and HF hospitalizations compared with placebo.[23] All these data suggest to initiate medical therapy early and probably before discharge, or as soon as possible during the following outpatient visits. However, as other large trials did not explore treatments starting in the hospital patients, most recent HF guidelines and recommendations are reluctant to recommend introduction of newly introduced oral HF therapies shortly after decompensation and during hospitalization, although continuation of introduced drugs during hospitalization and at hospital discharge is recommended.[12,15,53] This creates sometimes uncertainties of when to start in recompensated patients on incomplete therapies.

Chronicity of heart failure and outcomes

At the present time, optimization of guideline-directed chronic HF therapy remains the only definitive therapy for HFrEF patients to reduce early death and hospitalization. It is a matter of debate whether patients with longer duration of CHF are those who are better tolerating this condition or respond better to therapy and have prognosis or whether they are representing patients with long-standing clinical signs and symptoms with more advanced disease, higher non-cardiac co-morbidity load, and poorer outcomes. Data from the SHIFT trial have shown that the duration between the onset of HF signs and symptoms to treatment initiation has a substantial effect on clinical outcomes.[59] Patients with worsening CHF and long-standing symptoms, requiring mechanical circulatory support, had worse outcomes compared with acute or sub-acute HF.[60,61] In turn, better clinical outcomes were observed in HF patients receiving cardiac resynchronization therapy early after developing symptoms compared with those with longer symptoms duration.[62]

Heart failure is associated with a high burden of cardiac and non-cardiac co-morbidities,[8,16] and HF patients with co-morbidities such as chronic kidney disease or diabetes are at higher risk.[8,12] It has been demonstrated that a longer duration of CHF was associated with a higher burden of

Figure 3 A schematic scheme of the association of outcomes, treatment initiation, missed opportunities, and potential benefits of early intervention in heart failure patients. Data taken from Böhm *et al.*[59]



co-morbidities[59] and the number of co-morbidities was associated with worse outcomes.[60] This question has recently been confirmed in a *post hoc* analysis from DAPA-HF trial.[24,63] In this analysis, patients with longer HF duration had higher rates of worsening HF and death. Additionally, these patients were older with more co-morbidities. Interestingly, patients with a longer HF duration in SHIFT[59] and DAPA-HF[24] had a similar relative risk reduction with ivabradine and dapagliflozin, respectively, and a greater absolute risk reduction, compared with those with more recently diagnosed HF.[59,24] For these reasons, HF therapy should be optimized as soon as possible, as those with a longer HF duration might benefit at least as well. This might apply not only to drug therapies but also to implantable cardioverter defibrillator as even in later stages the risk of sudden cardiac death remained the same with shorter or longer duration of HF.[64]

There is an emerging discipline of 'implementation science' founded on the idea that advances and positive trials in HF have little meaning if not widely implemented. Treatment of HFrEF has become complex, and few patients get the opportunity to benefit from the wide array of treatments indicated in all or some patients. These include the four foundational HFrEF drug classes that were effective in reducing morbidity and mortality even at low starting doses, namely, angiotensin receptor neprilysin inhibitor, beta-blockers, mineralocorticoid receptor antagonist, and sodium–glucose co-transporter-2 inhibitors.[65] Notably, a significant benefit of these foundational treatments was apparent within the first 30 days after randomization,[66–68] and subsequent therapy with all four drug classes should therefore be achieved within 4 weeks.[65] Furthermore, an additional approach, which might play an important role in saving time in all HF outpatients, is hemodynamically guided pharmacotherapy with devices such as the pulmonary artery pressure sensor, which has been shown to reduced HF hospitalization risk, irrespective of left ventricular ejection fraction.[65,69,70]

This complex array of therapy combined of medications and devices is at odds with how HF care is organized in many countries, with delays in follow-up and poor access to cardiology specialists.[71,72] Indeed, emerging studies are showing that the main factors associated with non-use of evidence-based HFrEF therapy include not only higher age and co-morbidities but also acute care and chronic follow-up by non-cardiologists, lower socio-economic status as measured by education, income and marital status, and care provided in smaller town, rural, and non-university medical centre settings.[71,72]

Conclusion and future directions

Heart failure is an urgent clinical scenario along all its stages and disease conditions. Therefore, rapid management plays a significant role throughout the entire patient's journey. Prompt recognition of AHF patients in the ED and early initiation of therapy is in our view a mandatory step for improving in-hospital outcomes in acutely decompensated patients (*Figure 3*). Moreover, oral HF therapy should be started and optimized as early as possible after recompensation of patients and likely even before discharge, regardless of severity or duration of HF. Improving strategies to identify patients at

risk, optimize HF therapy, and develop follow-up methods is a beneficial, productive, and cost-effective approach to reduce economic burden of HF and improve outcomes. Time lavished before treatment initiation is recognized as important modifiable risk factor in HF! This is not really a very novel wisdom:

Defer no time, delays have dangerous ends.[25]

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Conflict of interest

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